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The Role of Esophagoscopy in Diagnosis and Management of Esophagitis in Children With Cancer

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Esophagitis is a common complication in patients treated for cancer; however, difficulty in determining its etiology on the basis of noninvasive clinical information limits the implementation of specific therapies. We reviewed our experience with esophagoscopy and biopsy as an aid in the diagnosis and management of esophagitis in children with cancer. Of eleven episodes of esophagitis evaluated by esophagoscopy with biopsy, four (36%) had an infectious etiology (two with Candida, one with Herpes simplex virus, and one with viridans streptococci). The absolute neutrophil count, presence of oropharyngeal colonization, and appearance of the esophagus at esophagoscopy were not predictive of the etiology of esophagitis. Esophagoscopy with biopsy affected the management of 4 (36%) patients. We believe this procedure to be a valuable aid in managing esophagitis in children with cancer by providing objective data not otherwise available to the clinician. **Med. Pediatr. Oncol. 28:299–303.**

Key words: esophagitis; esophagoscopy; immunocompromised; neutropenia; cancer

INTRODUCTION

Esophagitis, a common complication in immunocompromised patients such as those being treated for cancer, is most often manifested by odynophagia, dysphagia, or epigastric pain [1–4]. Esophagitis is a clinical diagnosis and often is treated empirically. Known causes in patients with cancer include chemotherapy, radiation therapy, gastroesophageal reflux, protracted emesis, and infections. Mucosal breakdown from chemotherapy or radiation therapy is postulated to render the esophagus susceptible to further damage by acid reflux and subsequent colonization with microorganisms. The most common infectious agents are *Candida* species and Herpes simplex virus (HSV) [1–7]. In bone marrow transplant patients and patients with the acquired immune deficiency syndrome, cytomegalovirus (CMV) is a significant cause of infectious esophagitis [8,9]. Less commonly reported cases include *Aspergillus* sp. and other fungi, varicella zoster virus, and a variety of bacteria [8,10].

Because clinical findings do not provide a reliable means of either distinguishing infectious from noninfectious causes of esophagitis or identifying the type of infection, a therapeutic ''shotgun'' approach is often used. This may include a variety of antimicrobial agents combined with therapies for reflux esophagitis. In adults, esophagoscopy with biopsy is a safe and reliable method of determining a specific etiology of clinical esophagitis, allowing more specific and definitive therapy [7,8]. Similar data in immunocompromised children has not been published. We reviewed our experience of esophagoscopy with biopsy in children with cancer in order to evaluate its utility and impact in the diagnosis and management of esophagitis in this patient population.

PATIENTS AND METHODS

Patients

The medical records of 57 patients undergoing 69 upper gastrointestinal endoscopies at St. Jude Children's Research Hospital between January 1991 and December 1993 were reviewed. Patients selected for this study met the following criteria: a) a primary diagnosis of either a hematologic malignancy or solid tumor, b) a diagnosis of clinical esophagitis as evidenced by one of the following: dysphagia, odynophagia, and/or retrosternal or epigastric pain, and c) esophagoscopy with biopsy sent for histological evaluation and/or culture. Patients with human immunodeficiency virus infection were excluded. Data collected from patient charts included demographic data,

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primary, and secondary diagnoses, use of chemotherapy and radiation therapy, hematologic parameters, presence of mucositis, use of antibiotics, use of corticosteroids, routine surveillance cultures, clinical symptoms of esophagitis, findings on esophagoscopy, complications of esophagoscopy, results of esophageal biopsy, and therapy for esophagitis.

Esophagoscopy, Biopsy, and Culture Methods

Esophagoscopies were performed by one of two staff gastroenterologists using an Olympus XP20 flexible endoscope. In each case the entire esophagus was visualized and described in detail. In most cases biopsy specimens from abnormal areas were sent for both histologic evaluation and culture. Tissue specimens were examined with hematoxylin and eosin, Brown and Brenn, Gomori methenamine silver nitrate and periodic acid-Schiff stains to identify bacteria and fungi, and with an immunohistochemical stain for HSV. Biopsy specimens were cultured on routine bacteriologic media as well as brain-heart-infusion broth with gentamicin (Edge Biologicals, Memphis, TN) for fungi, and an MRC5 cell line (Viromed Laboratories, Minneapolis, MN) in both tube and shell vial for HSV and CMV. Infectious esophagitis was diagnosed when either histopathologic evaluation or culture revealed the presence of microorganisms.

Statistical Analysis

The relationship between clinical laboratory features (absolute neutrophil count [ANC > or $\leqslant$500 polymorphonuclear leucocytes and band forms/cu.mm.] oropharyngeal flora, and the presence of mucositis) and the diagnosis of infectious vs. noninfectious esophagitis was analyzed by Fisher's exact test.

RESULTS

Ten of 57 patients (representing 11 of 69 endoscopies), ages 6 to 21 years of age (median age 14 years), met the study criteria. Excluded patients underwent endoscopy for reasons other than symptoms of esophagitis, such as acute gastrointestinal bleeding or evaluation of graft-versus-host-disease and were thus not included in this study. Demographic and laboratory data are shown in Table I. Infection was identified in 4 of the 11 episodes of esophagitis (36%). These were comprised of *Candida albicans* in two cases, HSV in one, and viridans streptococci in one. In each case the organism grew from the biopsy specimen, and in three cases histologic evaluation confirmed the culture results. Although three specimens grew bacteria, only the specimen that contained histologically evident gram-positive cocci (in a patient with radiation esophagitis) was categorized as true bacterial esophagitis. Of the remaining 7 episodes of clinical esophagitis, 5 were compatible with reflux esophagitis, and 2 showed normal esophageal tissue by histologic examination (Table I).

In the five esophageal biopsies with histologic features of reflux, there was epithelial hyperplasia with a thickened basal zone and elongated lamina propria papillae. Chronic inflammation with exocytotic lymphocytes was present in all five biopsies, and neutrophilic infiltrates were identified in one. In two cases, mucosal erosion and epithelial necrosis were present; one of these ulcers also contained colonies of gram-positive cocci. The squamous epithelial cells in all of these cases showed reactive atypia, with nuclear enlargement, mild pleomorphism, and prominent nucleoli. In one additional patient, the biopsy contained invasive blastoconidia and pseudohyphae, compatible with candidiasis. In another patient, epithelial cells contained ''ground-glass'' nuclei, and multinucleated cells were evident; these features are typical for herpes simplex. The morphologic diagnosis of herpetic esophagitis was confirmed by immunohistochemical stains for herpes simplex type 1.

Clinical features and laboratory data, including the absolute neutrophil count (ANC; number of polymorphonuclear cells plus band forms/cu mm), oropharyngeal flora, mucositis, and visual findings at esophagoscopy (Table I), could not be correlated with the presence of infectious esophagitis. The presence of neutropenia (ANC $\leqslant$500/cu mm vs >500/cu mm) did not predict a higher risk of infectious esophagitis ($p = 1.00$). Fungal colonization of the oropharynx did not predict the presence of fungal esophagitis ($p = 0.24$) with 8 patients colonized with fungus (4 with infectious etiology of their esophagitis and 4 without an infectious etiology) and 3 with no fungal colonization (all with a non-infectious etiology of their esophagitis). Likewise, the presence of oropharyngeal mucositis could not be correlated with infectious esophagitis ($p = 1.00$) with mucositis noted in 2 patients with an infectious etiology and 3 patients with a non-infectious etiology as compared to no mucositis in 2 patients with an infectious etiology versus 4 patients with a non-infectious etiology. Visual findings recorded in detail at esophagoscopy, including the presence or absence of inflammatory changes, plaque lesions, and ulcerative lesions did not predict the finding of infectious esophagitis. A barium esophagram was obtained in only one case (4a) and was normal. Clinical management was altered in 4 of 11 episodes (36%) as a result of information obtained from the biopsy specimens. This information prompted institution or continuation of appropriate therapy, or the discontinuation of inappropriate therapy (Table II). There were no complications resulting from esophagoscopy in our patients.

TABLE I. Demographic and Laboratory Data for 11 Episodes of Clinical Esophagitis in 10 Children With Cancer Undergoing Esophagoscopy With Biopsy

Pt #	Age (y)/sex	Underlying condition	ANC	Oropharyngeal flora	Oral mucositis
1	11/F	AML in relapse	<100	*Candida albicans*	Yes
2	10/M	ALL in relapse	<100	*Candida albicans*	Yes
3	15/F	ALL in relapse	<100	NG	Yes
4a	21/M	ALL-AML S/P Allo BMT	<100	*Candida albicans*	Yes
4b	21/M	ALL-AML S/P Allo BMT	>500	*Candida albicans* *Citrobacter freundii*	No
5	6/F	ALL S/P Allo BMT	>500	*Candida albicans*	No
6	18/F	CML S/P Auto BMT	>500	*Candida albicans*	No
7	10/M	AML S/P Allo BMT	>500	NG	No
8	14/F	Osteosarcoma of pelvis	<100	*Torulopsis glabrata*	Yes
9	18/F	PNET of chest	100–500	*Candida albicans*	No
10	16/F	Adrenocorticocarcinoma	100–500	NG	No

Pt #	Clinical impression prior to EGS	Visual findings of EGS	Histologic diagnosis	Culture of biopsy
1	Candida	Erythema; plaque	Reflux	*Candida albicans*
2	Reflux	Erythema	Herpes infection	Herpes simplex virus
3	Candida	Erythema	Reflux	NG
4a	Candida	Plaque	Normal tissue	NG
4b	Candida	Erythema; plaque	Candidiasis	*Candida albicans* *Citrobacter freundii* *Enterobacter faecalis*
5	Graft vs. host disease	Erythema	Reflux	Not done
6	Graft vs. host disease	Erythema	Reflux	NG
7	Varicella	Erythema	Normal tissue	NG
8	Candida	Erythema; ulceration	Reflux	NG
9	Radiation	Erythema	Gram-positive cocci infection	Viridans streptococci
10	Not specified	Normal esophagus; gastric ulcers	Reflux	Viridans streptococci

ANC = Absolute neutrophil count; EGS = esophagoscopy; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; BMT = bone marrow transplant; allo = allogeneic; auto = autologous; PNET = primitive neuroectodermal tumor; NG = no growth.

DISCUSSION

This retrospective review showed esophagoscopy with biopsy to be useful in clarifying the etiology as well as aiding in the overall management of symptomatic esophagitis in children and young adults being treated for cancer. The management of esophagitis in the immunocompromised patient is challenging, since possible etiologies are not readily discernable by noninvasive means. In adults, esophagoscopy with biopsy has proved to be a safe and reliable method of determining the etiology of esophagitis [4,7,8,11]. To our knowledge, a similar evaluation in children with esophagitis has not previously been done. Although our study sample was small, the results support the use of esophagoscopy with biopsy for the management of children with esophagitis.

In this study, an infectious cause was determined in 4 (36%) of 11 episodes, including 2 cases of Candida, and 1 each of HSV and viridans streptococci. This is consistent with studies in adults showing Candida and HSV to be the most common infectious causes of esophagitis

TABLE II. Impact of Esophagoscopy With Biopsy on the Managment of Children with Esophagitis

Management after esophagoscopy	Number of patient episodes	Patient number from table I
Changes in management		
Institution of appropriate therapy	2	2, 4b
Continuation of appropriate therapy	1	1
Discontinuation of inappropriate therapy	1	9
No change in management		
Continuation of empiric antifungal therapy despite lack of evidence of infectious esophagitis	3	3, 4a, 8
Continuation of existing management for noninfectious esophagitis	4	5, 6, 7, 10

[1–7]. Our overall rate of recovery of specific pathogens was lower than those reported in adult series (23–57%) [7,8,12], perhaps due to our small sample size.

In patients with oropharyngeal colonization with fungi, 50% were found to have an infectious etiology of their esophagitis in contrast to no infectious etiology determined in patients not colonized with fungi. Although the small numbers preclude any statistical validity to this issue it raises the issue of the utility of endoscopy in patients without fungal colonization. Other studies have found no correlation between presumed or cultured oropharyngeal flora and the results of histopathology and culture of esophageal biopsy specimens [7,8].

Most studies indicate that visual findings during esophagoscopy correlate poorly with biopsy results. Candidal esophagitis is thought to produce a plaque-like appearance, while HSV esophagitis is thought to cause bullae or ulcerations. However, it is generally agreed that these differences may be obscured in the latter stages of the disease process. Both of our patients with candidal esophagitis had inflammatory changes and plaque formation; however, our patient with HSV had only inflammation without bullae or ulceration. In addition, one patient with plaque had normal tissue on biopsy, and one patient with ulceration had reflux esophagitis. In a study evaluating the correlation of endoscopic changes with histologic findings in immunocompetent children, Biller et al. [13] found that the gross appearance of the esophageal mucosa failed to identify 30% of histologically proved cases of esophagitis. In addition, no specific endoscopic finding was predictive of esophagitis. Thus, it is essential that appropriate specimens be sent for histopathologic evaluation and appropriate cultures.

The goal of esophagoscopy with biopsy is to provide data helpful in the management of the patient. In this study, esophagoscopy did affect management in 4 of 11 episodes (36%). Although the presence of an infectious etiology always resulted in either institution or continuation of appropriate therapy, therapy was discontinued after culture results only once, a case in which amphotericin B was discontinued after viridans streptococcal esophagitis was diagnosed. Understandably, clinicians are less comfortable with the predictive value of a negative culture in the face of clinical esophagitis. Wheeler et al. [7] reported that esophagoscopy had a positive impact on the management of all 17 cases of infectious esophagitis. However, Vishny et al. [12] reported that esophagoscopy had little impact on the management of bone marrow transplant patients, most of whom received prophylactic acyclovir and were on systemic antifungal therapy for fever and neutropenia at the time of esophagoscopy. Furthermore, they were unable to identify any viral causes of esophagitis. However, because other studies in bone marrow transplant patients have shown that Candida, HSV, and CMV are significant causes of esophagitis [8], esophagoscopy is likely to be of value in these patients.

Complications of esophagoscopy include bacteremia or systemic infection resulting from the procedure, and gastrointestinal bleeding. In a review of published reports evaluating endoscopy with incidence of bacteremia, Brady et al. [4] calculated an overall incidence of 4.4% for bacteremia following endoscopy, with a range of 0 to 8%. More recently, Wheeler et al. [7] noted 3 episodes of fever following esophagoscopy, none of which were associated with bacteremia. No bleeding complications were noted in thrombocytopenic patients; three patients who underwent biopsies with platelet counts under 50,000/μL received concurrent platelet transfusions and did well. Vishny et al. [12] reported no complications in 48 endoscopies. In our study there were no episodes of new fever or bacteremia following esophagoscopy. We did not routinely obtain blood cultures following the procedure, nor did we routinely use antimicrobial prophylaxis at the time of the procedure. Seven patients with platelet counts below 80,000/μL were transfused with platelets just prior to or during the procedure, with no complications, a practice previously demonstrated to be safe [7,12].

In summary, esophagoscopy with biopsy in our experience has been a safe and important aid in the diagnosis and management of esophagitis in immunocompromised children. Esophagoscopy with biopsy provides objective data that would not otherwise be available to the clinician, resulting in a more definitive management plan for the patient.

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